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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/529,772

06/02/2005

William Alexander Denny

4450-14

1493

23117

7590

03/23/2009

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EXAMINER

KOSACK, JOSEPH R

ART UNIT

PAPER NUMBER

1626

MAIL DATE

DELIVERY MODE

03/23/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/529,772	<b>Applicant(s)</b> DENNY ET AL.	
	<b>Examiner</b> Joseph R. Kosack	<b>Art Unit</b> 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 08 January 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 3,4,8-11,16 and 19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 3,4,8-11,16 and 19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                      |                                                                   |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____                                                          | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 8, 2009 has been entered.

### ***Previous Claim Rejections - 35 USC § 103***

Claims 1, 3-4, 6, 8-11, 16, and 19 were previously rejected under 35 U.S.C. 103(a) as being unpatentable over Friedlos et al. (*J. Med. Chem.* 1997, 1270-1275) in view of Patani et al. (*Chem. Rev.* 1996, 3147-3176).

The Applicant has traversed the rejection on the grounds that compound 6 of Friedlos et al. is not sufficiently potent since it has an IC<sub>50</sub> that is lower than compound 1 of Friedlos et al., that it would require two structural modifications not suggested by Friedlos et al. to yield the compounds that are instantly claimed, and that Friedlos et al. teaches away from going to an asymmetric compound.

A declaration has also been provided from William R. Wilson to support the arguments and to attempt to show unexpected results.

The Examiner is not persuaded. Firstly, Friedlos et al. teach that they thought that the aziridine compound 1 was not useful clinically since human DT diaphorase is less efficient than rat DT diaphorase. This has absolutely nothing to do with IC<sub>50</sub>

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results. Therefore, it cannot be shown from the IC50 of compound 6 that compound 6 is “insufficiently potent.” Secondly, a full data set was not gathered for compound 6 of Friedlos et al. with respect to the T78-1 cell line with is NR negative. A showing that compound 6 was “insufficiently potent” with respect to the T78-1 line would actually be significant since the goal is to generate compounds which would selectively target the T79-A3 (NR positive) cell line.

As stated in the interview, Friedlos et al. teaches the required changes in order to yield compounds of the instant invention. Firstly, Friedlos et al. teaches that switching chlorine to bromine increases potency. See compounds 4 and 8, along with compounds 12 and 13 on page 1272. Secondly, Friedlos et al. teach that going from a symmetrical molecule to an asymmetrical molecule with a halogen and a mesylate group increases the selectivity for the T79-A3 cell line. See compounds 4 and 6 on page 1272. Therefore, the person of ordinary skill in the art would be able to envision the compounds of the instant invention. Additionally, this is proof that Friedlos et al. do not teach away from the instant invention.

The declaration by Wilson provides an intriguing result in compound 27744, which shows a 39 fold increase in activity for the T79-A3 with an increase in the selectivity. However, as discussed in the interview, the Examiner would like to see a comparison made to a compound that has the amide meta to the two nitro groups and a chloro and mesylate group on the mustard functionality. This would be helpful to determine whether the increase in potency is truly unexpected, or if the increase would be suggested through the suggestions of Friedlos et al.

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Therefore, as Friedlos et al. clearly suggests making the two changes to the compound 6 of Friedlos et al. to generate compounds of the instant invention and since the results presented in the Wilson declaration cannot yet be proven as unexpected, the Examiner is left with no choice but to maintain the rejection. The rejection is withdrawn for those claims expressly cancelled by the Applicant.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

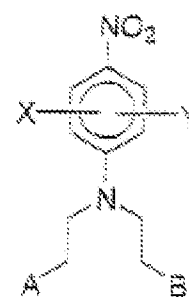
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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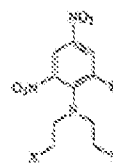
consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3, 4, 8-11, 16, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedlos et al. (*J. Med. Chem.* 1997, 1270-1275) in view of Patani et al. (*Chem. Rev.* 1996, 3147-3176).



The instant application is drawn compounds of Formula I: , their method of making, their method of use to treat tumors and cancer via GDEPT, and their use for the manufacture of medicaments.

Determination of the scope and content of the prior art (MPEP §2141.01)



Friedlos et al. teach compounds of the formula where R is CONH<sub>2</sub> and X and Y can be the same where they are halo. See Table 2 on page 1272. Friedlos et al. also details the method of making the halo substitution from the mesylate by reacting with a sodium halide in ethyl acetate. See page 1273, column 2. Finally, Friedlos teaches the method of treating of cancerous cells via GDEPT and a nitroreductase enzyme from E. Coli. See page 1274, column 2. As the compound is used as a medicament, the use of making a medicament is inherently described.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Friedlos et al. do not teach compounds in line with the proviso in which  $A \neq B$ .

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

Patani et al. teach that chlorine can be replaced by bromine or iodine. See page 3148, Table 3. This would yield 2-([6-(Aminocarbonyl)(2-bromoethyl)-2,4-dinitroanilino]ethyl methaneiodide.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention was made to follow the synthetic scheme of Friedlos et al. with the replacement suggested by Patani et al. to make the claimed invention. The motivation to do so is provided by Patani et al. Patani et al. teach the use of bioisosteric replacements to rationally modify lead compounds into safer and more clinically effective agents. See page 3147.

Thus, the claimed invention as a whole was *prima facie* obviousness over the combined teachings of the prior art.

**Conclusion**

Claims 3, 4, 8-11, 16, and 19 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph R. Kosack whose telephone number is (571)272-5575. The examiner can normally be reached on M-Th 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Joseph R Kosack/  
Examiner, Art Unit 1626